Meeting Minutes
EECA CAB
and ViiV Healthcare

October 22, 2014, Tbilisi, Georgia

Meeting participants

ViiV Healthcare:

Boris Charchyan, General Director, ViiV Healthcare Russia
Evgeniy Bukin, Medical Director, ViiV Healthcare Russia
Kakha Giorgadze, Medical Manager, GlaxoSmithKline, Georgia

EECA CAB:

	Name	Organization	Country
1	Ehtiram Pashayev	Community Association again AIDS	Azerbaijan
2	Yulia Kalancha	PEREBOI.NET.UA	Ukraine
3	Sergey Dmitriyev	All-Ukrainian PLHIV network, Kharkiv office	Ukraine
4	Nurali Amanzholov	Kazakhstan Union of People Living with HIV	Kazakhstan
5	Anait Arutyunyan	PLHIV Network of Armenia	Armenia
6	Artem Esse	Patient Control	Russia
7	Natalia Minayeva	My Home	Kazakhstan
8	Denis Marukha	PLHIV Leagus	Moldova
9	Alexandrs Molokovskis	HIV.LV association	Latvia
10	Dmitry Sherembey	Patients of Ukraine	Ukraine
11	Tatevik Tatulyan	PLHIV Network of Armenia	Armenia
12	Aisuluu Bolotbayeva	Central Asian HIV Fund	Kyrgyzstan
13	Yurgis Andryushka	Pozityvus Gyvenimas association	Lithuania
14	Sergey Biryukov	AGEP`C	Kazakhstan
15	Alexey Mikhaylov	ITPCru	Russia
16	Denis Godlevsky	AIDS Help Fund (AHF)	Russia
17	Grigory Vergus	ITPCru	Russia

Moderators: Alexandra Volgina, Tatyana Khan.

Beginning of meeting. Introduction of participants.

Minute's silence to commemorate those who passed away as HIV drugs had failed to reach them.

Presentation on drug-drug interaction

ViiV's portfolio includes a number of HIV drugs that also include integrase inhibitors. The first drug of this class registered in 14 countries is dolutegravir. The EECA CAB meeting participants had submitted a prior request on drug-drug interaction between dolutegravir and substitution therapy drugs.

Unlike most ARV drugs, dolutegravir is less metabolized by the P450 cytochrome system. Its main transformation route is metabolism through the UDF glucoraniltranferase system. This explains the drug's minimum quantity of drug-drug interactions, thus allowing the drug's molecule to circulate in the bloodstream intact. The drug is partially excreted by the kidneys, but the total quantity of drug thus excreted is very small.

The company conducted a lot of trials aiming to study the drug's pharmacokinetics for drug-drug interaction. On the interaction between dolutegravir and Methadone: the trials was conducted on healthy volunteers that were given methadone while on substitution therapy programs, and dolutegravir, the maximum allowable dose of 50 mg was given twice daily. The study results speak about dolutegravir's correction when using it with methadone. The presence of dolutegravir in the blood did not statistically influence the methadone concentration.

Question: Is there any data available on buprenorphine?

Answer: No individual trials were conducted, but given buprenorphine's pharmacokinetics accord with that of morphine derivatives, no significant statistical influences are expected.

The drug's registration in EECA countries

In May, the company gave EECA CAB an update on drugs' registration.

Today the company has plans for primarily submitting dossiers for pediatric drug formulations, as well as for the fixed dose combination Kivexa.

- In Armenia, the Kivexa dossier will be submitted by December this year. The pediatric dossier (Ziagen and Epivir suspension) have been submitted, marketing authorizations (MA) are expected to be issued in the next year.
- Georgia, Azerbaijan, Moldova – the coming-in and supply of the drugs are possible without an MA under Global Fund (GF) programs.
- Belarus, Kazakhstan – Kivexa and Ziagen and Epivir authorized for marketing.
- Kyrgyzstan – no authorization, dossier being developed (Kivexa, pediatric Ziagen and Epivir).
- Tajikistan, Turkmenistan – no company operations, all supplies via GF.
- Uzbekistan – dossier being developed (Kivexa, pediatric Epivir). Ziagen – authorization process over, reissuance in progress.
- Ukraine – all drugs authorized.

Question: GF is leaving Moldova in the next three years. What are the company's plans on drug authorizations?

Answer: In the first place, pediatric Ziagen and Epivir and Kivexa will be authorized. Then - dolutegravir, after it – the Triumeq combination. The dossiers are expected to be submitted in 2015.

Question: In Azerbaijan, the drugs are practically not procured on GF money; since 2015 the financing will be solely on state budget. The GlaxoSmithKline country office said the authorizations of dolutegravir, Kivexa and lamivudin were in progress.

Answer: The dossiers for Kivexa and pediatric Ziagen and Epivir are being developed now. In September, the dolutegravir dossier will be submitted.

Question: What's the pricing policy on pediatric forms in Armenia? And when will the authorizations be received?

Answer: No quotes on pricing policy so far. As soon as the Ministry of Health issues their request, the price will be considered. As soon as the MA is received, we will be able to expedite the timeframes for dossier submission, though not authorization completion. The duration of this process varies country-to-country (for example in Georgia – 3-4 months, in Russia it may last up to 1.5 years).

Question: What level of prices of the company drugs is expected in these countries after GF leaves?

Answer: There were almost no company drugs supplies via GF, GF money was mostly used to procure generics. The company can't compete with them on price. At the same time, generic companies do not make pediatric drugs. No procurements of pediatric forms took place in EECA countries; it could be Combivir, lamivudin, zidovudin, which the company is not planning to submit for authorization. Kivexa will be priced based on the country's income and epidemic level.

Question: What level of price of these drugs is expected in Azerbaijan?

Answer: We are not ready to say the price just yet. Income-wise, Azerbaijan is a middle country, like Russia and Kazakhstan, so the price should be expected subsequently. On pediatric forms – on the whole, they are not expensive, one of the drugs is about 20 US dollars.

Question: The Latvian example has showed that the company may very well compete with generics on price. The latest base price quoted on Combivir is 37 Euros. On Trizivir – since 1 July 2013 till today the company sold 6 packs of the drug in Latvia. Why isn't the price going down?

Answer: The Russian office does not cover the Baltics, so we already sent a request to our colleagues. Here is the deal. We can't compete with generics, but up to a certain limit. In Latvia the company competes with Sandoz, also a strong company on drugs quality. But in Russia the price of generic combivir by Hetero or Ranbaxy is about 10 Euro, so here we can't compete. On Trizivir, no request came from the Ministry of Health as to the need for bringing the price down. The price was registered a long time ago; there is no interest in the drug, so the company has not registered a new price.

Question: In Ukraine, a year-long treatment course of generic combivir is a hundred US dollars, and this price is cost-effective. Why doesn't the company quote the same prices, once the drug's patent is long expired?

Answer: A profitable business of 100 dollars is way lower than cost – for GlaxoSmithKline, Pfizer or Sandoz - because other different quality systems are involved here.

Comment: Can't be the cost of a ViiV drug is tenfold.

Company comment: Not tenfold, but yes, x-number-fold. It's worth remembering also, that when a drug loses its patent, it also loses the market volume, which is the key pricing factor. Cipla and Hetero supply generic combivir to a huge number of patients. The quantity of drugs ViiV may have manufactured for Russian and Ukraine is a minor amount, so the price would be several times higher.

Question: About Trizivir – how high is it as a company priority?

Answer: Trizivir has a pretty narrow scope of indications, it's not a key drug for the company. In Russia 1-2% of the patients are on this drug, mostly with an HIV-TB co-infection.

Question: Pricing policy decisions are taken based on the World Bank's data, but the real situation varies country to country. In Armenia, the number of patients is not large from the point of view of business, but they also need the treatment.

Answer: Armenia is in the group of countries with low/middle incomes, therefore the pricing policy for Armenia will be lower than for Russia, Kazakhstane and Azerbaijan. After receiving MA, the company will be ready to discuss the price by the Ministry's request.

Question: If a drug's patent expires in the near future, do you take a proactive position and suggest the generics manufacture the drug under company control? Is there any strategy of working with generic companies?

Answer: The company has been studying this issue 3 years, including a look at potential generic companies. This analysis is not only of equipment, but also checking on a company's finances and anticorruption inspection. No company passes this sort of inspection for different reasons. In Russia, for example, it's very difficult to localize a product. In Ukraine this situation is a bit better. The company has held a lot of negotiations but, unfortunately, our attempts weren't much success.

The strategy on patent-expiring drugs – the company are actively bringing the price down, so at the moment the patent is over, it gives the drug away to generics and takes other innovator drugs.

Question: Is the company ready to publish a list of requirements for generic manufacturers to enable companies to submit applications?

Answer: Any manufacturer may submit an application. These are publicly available criteria, we will inform you later where they will be published.

Comment: In Ukraine, there are pharmaceutical companies that can meet your requirements.

Company answer: We are interested in production localization in Ukraine and will appreciate if you share with them our contacts.

Question: Have you considered setting up a site for your own generic manufacturing in Poland, for example?

Answer: As was mentioned before, the production of drugs with expired patents is not profitable for us.

Question: As you have said, Kivexa is one of the company's priority drugs, but since January 2010 in Latvia and Lithuania its price stayed the same, while the sales are going up. Perhaps you have to think about bringing the price down?

Answer: This question will be forwarded to our colleagues responsible for the Baltics. The information will be provided in written form.

Question: Please mention the company's priorities on drugs.

Answer: Until recently, Kivexa was the top priority for adults, now it is Tivicay. Kivexa is in second position, but there is a new combination coming - with dolutegravir (Triumeq – Kivexa + dolutegravir) that is expected to supplant it.

Question: Please comment on the trial thing with the Russian abacavir analogue.

Answer: The situation is evolving. We are not ready to speak about the quality of the generic, but the company think it a violation of their rights, since the drug is still under the patent in Russia (till 2018). The case is being heard in Rospatent now, which will be followed by a copyright trial and arbitration.

Comment: By 2017, the Russian healthcare budget will be cut by 22.8%, while by 2020 – 640 thousand people are expected to be placed on medication – according to academician Pokrovsky. From experience – the appearance of two and more generics in 70% of the cases result in a substantial price reduction, thus providing treatment for more people. We encourage you to withhold litigations with generic companies, if they start marketing a generic drug 2-3 before the patent expiration.

Company comment: So far we don't see any great price economy. Also, trials don't prevent generic companies from taking part in tenders.

Question: Will you submit dolutegravir for its inclusion into the list of vital and essential drugs in Russia?

Answer: The drug's DOSSIER has been submitted, the company are expecting a decision for its inclusion in the Essential Drug list. Its price is expected to be lower than that of its direct competitor (NB. – raltegravir by MSD). From other markets' experience, as soon as dolutegravir was issued, raltegravir's price also went down, by about 20%.

Comment: In Russia, retaining combination drugs is a very critical point. Unfortunately, we more and more have the information that in the next year the trend of splitting combined forms will continue to save money. We encourage you to revise Kivexa's price to make healthcare administrators' life easier when it comes to providing a substantiation of procuring combined forms.

Company comment: Next year a full localization will be conducted on Ziagen and Kivexa in Russia, including tableting and further primary and secondary packaging. However, we maintain that the patient community is the key driver to retain the combined forms.

Question: Any company plans to authorize Triumeq in the region?

Answer: The plans include dossier submissions until late 2015 in all countries of the region except Tajikistana. In Russia this will come a bit later because by the country's law, clinical efficacy and safety trials are necessary in Russia. Now an ARIA trial is underway among the female population, first outcomes expected only in 2016.

Comment: There are areas and locations bringing pharma companies the most market share. The rest are not commercially attractive. Gilead came out with a new drug and at once furnished a voluntary license for a list of certain countries. Is it possible ViiV considers this kind of strategy?

Company comment: This is one of the strategies to improve access to drugs. The company has an agreement with the Patent Pool on abacavir and dolutegravir, which also includes part of the EECA countries, for example Ukraine was included in the agreement on pediatric abacavir and dolutegravir.

Question: Ukraine is not included in the agreements on adult forms because it's a referent country for Russia?

Answer: Ukraine is listed as a low-income country. Ukraine is not on that agreement because it's the World Bank's category. The company's pricing policy in Ukraine does not depend on that in Russia. In 2014 the Grivna exchange rate for drugs procurement was set on the level of 2013, thus abacavir's price in Ukraine was about 20 pounds per pack, in Russia – about 80 pounds. This price is the lowest among the countries with the same income level - according the World Bank.

Comment: Speaking about Ukraine, the overall budget deficit accounts for two country's budgets, while the healthcare allocations deficit is 70%. The reference to the World Bank's data does not look too convincing.

Question: What shall we do to help revise the decision to not include Ukraine in the adult abacavir agreement?

Answer: Write a letter with substantiations, point to the mistakes made, furnish your own model of calculations of some kind, etc. (NB. – a letter to Boris Charchyan and the company's Ukrainian office). The company has already received such a request, and gave an answer to it (NB. – a letter from EECA CAB, March 2013 http://eeca-cab.org/ru/3/), which was negative. But you can write another letter – with stronger substantiation points.

Comment: Yet we would like to encourage the company to be more socially responsible and take a more proactive position.

Company comment: We are not quite ready to take the criticism on this issue. To give Ukraine such an unprecedented price, the question would be raised on the topmost level. The prices of Ziagen and Kivexa in Ukraine are on the level of developing countries, where the situation is far worse. We can promise that dolutegravir's price in Ukraine will also be discounted.

Question: What's the situation about the hypersensitivity for abacavir and tropism tests for maravirok?

Answer: Let me start with Russia. The company have been cooperating a number of years with an NGO gathering needs from AIDS centers as to the abacavir hypersensitivity tests. Last year we passed about 10 thousand kits for testing all patients who might have started therapy

in 2013. In 2014, we will provide about the same number of tests. Concerning the tropism test for maravirok – as early as in 2012 the company organized a system for sending blood samples for this test in a central specialized laboratory. The federal centers having a lab site to do this test received those tests from us in 2013. If in this year requests are made to get these tests, the company are ready to give them. Today more than a thousand people have passed a tropism test in Russia.

Question: In Russia maraviroc300 mg costs about 23-26 thousand rubles per pack (NB. – about 600 US dollars at the time of the meeting). Can you leverage the pricing process by the distributors?

Answer: That's the purchasing price from the distributor, but the AIDS centers are aware of the company prices (about 19 thousand RUR per pack 300 mg), so we believe they may quote lower prices.

Comment: This drug is not part of the Vital and Essential list, subsequently, it has no maximum allowable price. The distributors are coming with their proposals, which is how the initial maximum price is built.

Company comment: AIDS centers may also ask the manufacturer about the price to do a cross-check of the price they got from the distributor. As an option, AIDS centers may announce an auction on the price from the manufacturer, so in this case the company may influence the distributor. Otherwise, we cannot influence the distributor's policy.

Question: What's the maraviroc and tropism test situation in the region countries?

Answer: The authorizations are granted to maraviroc in Ukraine and Kazakhstan, indication – use in patients with ARV therapy experience – unlike the Russian indications. On this test, the company is cooperating with InterLabService, they are ready to supply test systems to Ukraine and Kazakhstan. In Ukraine the test has been submitted for registration, in Kazakhstan the test may be brought over without an authorization. An urgent need be for maraviroc – there are good connections in Germany, so in this case the test can be brought over without much problem. The issue is that there's not much interest in this drug by medical community.

Question: The example of combivir – in the auction documentation some distributors also submit combination drugs and monocomponents. What's your position on this issue?

Answer: Our position is combined drugs regardless of the manufacturer; in principle, we don't want to see monodrugs in the lots for procurements of lamivudin/zidovudin.

Question: You said your proposals are gotten by all procurers in Russia. How does it happen?

Answer: We send our proposals reactively, upon AIDS centers' requests. Proactively we can't do this according to the company's in-home policy.

Question: Speaking about the other countries doing their procurements on state money, it that the same pattern?

Answer: The pattern looks similar, since the drug's prices are authorized by the state. But often this is outdated data, a lower price may be provided upon a request.

Question: You mean a request to the Russian company office?

Answer: Yes. Requests may be also sent to GlaxoSmithKline country offices, but they are anyway forwarded to the Russian office, since the Russian office is responsible for the region.

Question: This is about the company policy on distributors. If the patient community sees overpricing by distributors, what steps should be taken to help you shed light on the situation and contribute to it?

Answer: The company has a pretty tough system of dealing with the distributors. The company has no legal leverage as applied to them, since the contract has no terms to penalize a distributor for overpricing. If you see an overcharge and AIDS center has announced, we may not confirm the distributor's participation in this tender, so the bidding may be postponed.

Comment: A proposals' withdrawal would normally cause delays in shipments.

Company comment: This is why it's important to respond before a withdrawal.

Question: In Russia they often have issues with shipment deadlines, so they don't deliver the drugs in time.

Answer: Unfortunately, in Russia shipment deadlines are set by the purchasing agent, so the companies are often faced with a shortage of necessary stocks at the warehouse. When there was centralized procurement, there were clear auctioning schedules, supply deadlines and approximate volumes. The remaining shelf life is also some challenge. The pediatric drugs we spoke about can be stored 2 years, so the manufacturer can't bring over a big lot, since most AIDS centers claim a remaining life of 70%. There's nothing you can do about it, unless you are informed on long notice about a procurement-to-be. Also, far not all purchasing agents are ready to buy drugs with a 50% remaining shelf life, feeling difficult to replace drugs even on our warranty, if they fail to sell them by the expiry date.

Comment: Back to the prices of drugs in Latvia. I believe in other countries of the region the trend is about the same. For Kivexa, this is 862 packs sold in 2010 in Latvia, in 2013 it was 2936 packs, over the 7 months of 2014 – 2543. Unfortunately, there is no data on packs, but there is the number of prescriptions issued. In 2012 - 57 prescriptions were issued, in 2013 – 949, six months of 2014 – 653. The price remained the same. In Latvia, the baseline compensation price is 369 Euro, in Lithuania – 371, with the drugstore's premium, VAT etc. The country office is not ready to discuss prices, so please consider an opportunity for price reduction.

Company comment: We'll clarify the situation and what company prices there were in those countries.

Question: Do you have an auction monitoring system in Russia?

Answer: We have an employee monitoring auctions, we monitor about 80-85% of the auctions.

Question: If this person sees an overcharge at an auction, can you respond to this situation?

Answer: 90% of the Kivexa tenders in Russian ran below the company price lists. These might have been those on maraviroc, but once the bidding's opened, it's too late to respond.

Question: In Russia the prices of pediatric drugs are going up. Any rise by the company in this year?

Answer: No. No upward adjustments were considered since 2010.

Question: This question is about Combivir. We asked you to provide the minimum public price of this drug which, as you have mentioned, is 1000 rubles per pack. You maintain this information is only available upon request made by an AIDS center. Can this information be provided upon our request? The company's Combivir share in Russia is about 5%, so it's clear the company are not interested in it anymore. But we are interested to procure the drug and its analogues at this minimum price. Every time we would see an auction with a price over 1000 rubles, we would show them this letter from you. This would be good for other countries too, as well as for yourselves – the company brings the price down, while civil society keeps track of it.

Answer: Normally this information is provided upon an AIDS center's request. All 2013 and 2014 we keep responding AIDS centers informing them there is such a price. About your request – the company is working with prescribed drugs, so we need to consult with the legal advisors.

Comment: In our opinion, the company should terminate the agreements with the distributors regularly overcharging. If we see this behavior of the distributors again, we assume it's the pharma company's liability.

Company comment: The company policy brings these risks to a minimum level. As was mentioned already, 90% of the tenders ran below the price list level. The company is doing its best. Last time the EECA CAB meeting had a lead on a distributor's poor performance; in this year the company has no contract with them. This time we took this maraviroc overcharge signal into consideration.

Question: Can a letter from a patient organization on overcharging be the reason for terminating the agreement with the distributor?

Answer: Yes. It must be official with a detailed description of the situation.

Comment: About the prices. As an option – many countries have country coordination mechanisms which include representatives of civil society. Perhaps, they should have information on the baseline prices.

Question: When we speak of leveraging distributors – can this be an appendix to the agreement with detailed actions in case of a distribution overcharge?

Answer: We will claim independent legal advice on this issue.

Question: My question is about new developments, including cabotegravir, which may have a good capacity in HIV treatment and prevention.

Answer: We would like to talk about the company developments on the whole. The first step has already been made – the dolutegravir registration. The next step is deriving drugs from dolutegravir – one pill once daily. The company is starting active cooperation with Janssen which will include studying integrase inhibitors combined with new generation NNRTI. The efficacy of dolutegravir and rilpiviripine will be studied in patients after induction of viral supression. Cabotegravir is also being developed (drug 744) – in two forms – tableted and injectable. The injectable may potentially be used as pre-exposure in discordant couples and post-exposure as prevention, and as treatment. The first results have shown that potentially injections can be given less often – once a quarter.

Special development program include trials in patients with renal insufficiency, concomitant infection (viral hepatitis, TB), and pediatric drugs. Within two years we are expecting outcomes from dolutegravir use in children aged 4 weeks to 18 years old.

Question: did I get you right 744 injectible is a full-fledged therapy not requiring a daily intake of pills?

Answer: In combination with injectible rilpivirin - yes. This is not therapy inception. It's about the patient reaching an undetectable viral load, after which the patient may be transferred to one injection every three months. Now Phase IIb is running out, which is to be expected 5-6 more years. About supporting therapy – now Russia is being considered to be one of the countries for studying the use of combination of dolutegravir plus rilpivirine pills (2015). There are very few API's there, 50 mg dolutegravir and 25 mg rilpivirin, which will make a positive contribution to treatment adherence.

Question: EECA CAB would like to take part in designing your clinical trials planned in our region, is there such an opportunity?

Answer: This is a question for the company legal advisors, but we will consider this opportunity.

Comment: We would like to ask you to continue developments of injectible forms for naïve patients, given the high level of the epidemic amongst injectible drug users which are difficult to retain on treatment.

Answer: If the drug passes all trials, it will be pretty easy to transfer it for use by naïve patients.

Question: What's the situation with developing pediatric forms?

Answer: The trials are underway for dolutegravir, including one on the use of the combined form. Also, two years ago the company concluded an agreement with Mylan Pharmaceuticals, an American company, on a dispersable form of Kivexa, by 2018 we expect to complete development of this pediatric formulation.

Question: About the company drugs' authorization in Georgia. Two drugs (trizivir and ziagen) are expiring their authorization deadlines, what's the company policy on this matter?

Answer: The company's priorities include the pediatric ziagen and epivir, and adult kivexa. If necessary, we can solve the issue with Trizivir, but the demand for it wasn't very big. An authorization just out of doing it makes little sense.

Question: How do you tell a need for a drug?

Answer: Over the 5 years when the drug was registered, it wasn't practically used. If necessary, the supply could be without an authorization (By Georgian law, you can bring over up to 10 packs with a prescription).

Question: Were there any supplies of your drugs to Crimea?

Answer: We don't quite understand how the procurement is and will be going on in Crimes. The latest Crimea supply activities date back to March of this year, if you have an update, please share.

Question: Many rumors have it it's possible to return to a centralized procurement system in Russia. How do you estimate your odds in a centralized system compared to generics?

Answer: We have already said we were not competing with generics on drugs with expired patents, so we hope they will be able to provide patients with drugs. However if this doesn't happen, we are ready to bring into the country the right amount of the drug. If you see the centralization and decentralization as a whole, it's got a number of pluses and minuses. The biggest minus is that there will be either less or none at all combination drugs. Regional procurements allowed us to consider not only the economy, but also adherence issues. The main advantage of centralization would be the opportunity to plan beforehand the quantities, supply timeframes, etc. Though in the current situation it is also possible, once AIDS centers are obliged to call for auctions from March to May, and fix supply terms in three months after signing the agreement. We are fine with any system that works in the interests of the patient.

Question: In what countries of the regions does the company do its clinical trials? Is Moldova on the list of these countries?

Answer: First and second phase trials include the European region and America, due to strong experience and potential of investigational sites and the simpler legislations. Third phase will also be conducted in the countries of the region, including in Russia. The dolutegravir trials involved over 40 countries. All information is available on clinicaltrials.gov. No trials have been conducted in Moldova yet; the legislation there only allows for IV phase trials.

Comment: This is about the countries where GlaxoSmithKline is doing authorizations. The impression is in some countries the authorization issue is far from being their top priority.

Company comment: ViiV is owned by GlaxoSmithKline. Andrew Witty, the company's first person, has pinpointed the company's four priorities in the world: respiratory, vaccines, rare diseases and HIV. If somebody doesn't understand the company priorities somewhere, we would like to know where it is going on. We will appreciate if you brief us on that.

End of meeting.